Total parenteral nutrition on energy metabolism in children undergoing autologous peripheral blood stem cell transplantation

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Abstract: The resting energy expenditure (REE) and the respiratory quotient (RQ) were measured longitudinally using indirect calorimetry to examine the effects of total parenteral nutrition (TPN) on energy metabolism in children undergoing autologous peripheral blood stem cell transplantation (PBSCT). There were six children (two males and four females) and the age ranged from five to 13 years (median, eight yrs.). The diagnosis included acute lymphocytic leukemia (ALL ; 4), neuroblastoma (NBL ; 1) and primitive neuroectodermal tumor (PNET ; 1). TPN was started after the patients were stabilized following PBSCT (group A ; n=3) or before the initiation of high-dose cytoreductive chemotherapy (HCC) (group B ; n=3). Duration of HCC before PBSCT was identical between the two groups (six to eight days). Average total calorie and protein intake during HCC was significantly higher for group B than for group A. The %REE, the percentage of REE to the predicted basal energy expenditure (BEE), in group A showed 133±19%, 129±14% and 146±11% during three periods of HCC (days -8 to -1 of PBSCT), bone marrow suppression (days 0 to 11 of PBSCT) and bone marrow recovery (days 12 to 22 of PBSCT), respectively. In contrast, those in group B were 10% to 20% lower than those in group A at all periods. Carbohydrate oxidation rates during HCC in group A were significantly lower than those in group B, and those were not different between both groups during post-PBSCT periods. Fat oxidation rates in both groups were similar at all stages of periods. In contrast, protein degradation rates in group A were significantly higher than those in group B at all stages of the period. From these results, we concluded that commencement of TPN administration prior to HCC in the patients undergoing PBSCT provides beneficial effects to maintain better energy metabolic and nutritional status. J. Med. Invest. 44 : 199-203, 1998

Key Words : *total parenteral nutrition, peripheral blood stem cell transplantation, resting energy expenditure, respiratory quotient, nutritional support*

INTRODUCTION

High-dose cytoreductive chemotherapy (HCC) in conjunction with autologous peripheral blood stem cell transplantation (PBSCT) is increasingly used for the treatment of children with acute leukemias and advanced solid tumors (1, 2). Although the direct and immediate effects of HCC on energy metabolism are variable and poorly documented, this procedure is commonly associated with severe mucositis and anorexia (3, 4), and resultant malnutrition contributes to a reduced tolerance to therapy and is associated with increased susceptibility to infection (5). Furthermore, nitrogen loss occurs both as a result of enteritis and as a direct result of the catabolic effect of HCC : it is compounded by relative immobilization, infection and graft-versus-host disease (6). Hence, nutritional support for children undergoing PBSCT needs to be closely integrated in the comprehensive protocol for improved therapeutic results (7, 8).

The resting energy expenditure (REE) in children reflects changes in body composition resultant of malnutrition or intermittent semistarvation (9, 10). To complete PBSCT relatively safe, intense nutritional support which includes measurement of the REE and the respiratory quotient (RQ) using indirect calorimetry, may become mandatory. In this study, we attempted to examine the nutritional

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status and the impact of timing of the start of total parenteral nutrition (TPN) on energy metabolism in children undergoing HCC and PBSCT.

MATERIALS AND METHODS

Patients

Six patients were enrolled into the study. The patients aged from five to 13 years (median, eight yrs.) received HCC and PBSCT for acute lymphoblastic leukemia (ALL ; n=4), neuroblastoma (NB ; n=1) and primitive neuroectodermal tumor (PNET ; n=1) [Table 1]. They were divided into two groups according to the timing of the TPN commencement. TPN was initiated after HCC in group A (Patients 1, 2 and 3), or prior to HCC in group B (Patients 4, 5 and 6). Duration of HCC before PBSCT was identical between the two groups. Duration of HCC ranged from six to eight days. Therefore, patients in group B were administered TPN for approximately one week longer than patients in group A.

Peripheral blood stem cell transplantation (PBSCT)

Peripheral blood stem cells (PBSC) were collected two to three weeks following completion of the consolidation chemotherapy, which were variable regimens depending on patients disease, and stored in liquid nitrogen until use as previously described (1, 2). HCC consisted of 450 mg/m^2 ranimustine (MCNU), 1,600mg/m^2 etoposide (VP-16), 16g/m^2 cytarabine (Ara-C) and 100mg/kg cyclophosphamide for patients1, 2, 3, and5. And 800mg/m^2 etoposide, 1,600mg/m^2 carboplatin, and 180mg/m^2 melphalan were administered for patients 4 and 6. Following HCC, patients were infusen with frozed-thawed PBSC which had been collected after consolidation chemotherapy. Supportive care included patient isolation in a hospital room equipped with a laminar air-flow system, infection prevention with intravenous acyclovir and immunoglobulin. Red blood cells were transfused to maintain a hemoglobin level over 7g/dL, and prophylactic platelets were transfused to maintain a platelet count over 20 x 10^9/L

Total parenteral nutrition (TPN)

A central venous (CV) catheter was inserted in all patients prior to HCC, and TPN was administered through the CV catheter. TPN was initiated with approximately 12% to 15% glucose concentration and increased up to 25% to 30% for two to three days as tolerated. One to 2.5g/kg of amino acids was administered with standard adult amino acid solution (Aminic, Morishita Co. Tokyo, Japan), and 250mL of 10% fat emulsion (Intrafat, Otsuka Pharmaceutical, Tokyo, Japan) was given twice a week. Accordingly, TPN supplemented patients with 37.0 to 83.2kcal per kg of body weight daily. Other additives included electrolytes (sodium chloride, calcium gluconate, magnesium sulfate), trace elements (iron, manganese, zinc, copper) as trace element preparations (Mineralin, Nippon Pharmaceutical, Tokyo, Japan), and vitamins (vitamin A, B_1, B_2, B_6, C, D, E, nicotinamide) to meet the maintenance nutritional requirement.

Metabolic abnormalities including electrolyte and glucose levels and liver function were checked at least twice weekly during the TPN administration. Weight was followed daily in all patients during treatment periods. Parenteral and oral intake are recorded daily. Management of CV catheter included daily sterile care for the catheter entrance and exit sites.

Energy-metabolism studies

The REE was studied using open-circuit indirect calorimetry (Calorie Scale, Chest MI, Tokyo) employing a transparent ventilated hood system at various periods of transplant. The system was calibrated before each test with a reference gas mixture (95% O_2 and 5% CO_2). The REE was measured for 20min at 8 : 30 under the fasting condition. Energy expenditure was calculated from the respiratory gas exchange using a standard equation (9). The RQ and protein oxidation were calculated from measurements of daily urinary nitrogen excretion. Urinary nitrogen production was calculated from measured or estimated daily urinary urea elimination (11). Fat and carbohydrate utilizations were calculated from the nonprotein RQ (9). The recommended dietary allowances for Japanese individuals were used to calculate predicted basal energy expenditure

Table 1. Clinical and nutritional findings of the patients

	Group A			Group B		
	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6
Diagnosis	ALL	ALL	ALL	NB	ALL	PNET
Age (years)	8	8	8	5	13	5
Sex	M	F	M	F	F	F
Body height (cm)	121.0	126.7	125.0	112.0	150.5	112.0
Body weight (kg)	22.1	23.5	23.6	19.3	50.5	16.8
% of ideal body weight (%)	82.8	89.6	89.4	102.8	106.5	89.5
Rohrer's quotient	124.7	115.5	120.8	140.9	148.1	119.6
BEE (kcal/day)	922	881	984	940	1465	818

ALL : acute lymphoblastic leukemia, NB : neuroblastoma, PNET : primitive neuroectodermal tumor
BEE : basal energy expenditure

(BEE). The percentage of REE to BEE was shown as % REE. After an explanation on the purpose, design and meaning of this study, informed consent was obtained from these patients and their parents at least one month before PBSCT treatment.

Statistical analysis

Results are expressed as means±SD. Student's t-test was performed to assess significant differences between individual groups. The significance level was set a priori at $p<0.05$.

RESULTS

1. Nutritional and metabolic status of the patients

Marrow aplasia, defined as less than 1,000 absolute neutrophils (ANC) per mL of peripheral blood, continued for 9 to 13 days (median, 11 days) after PBSCT. TPN stopped after sustained bone marrow recovery on 22 to 25 days following PBSCT. Therefore, patients in groups A and B were administered TPN for 15 to 23 days (median, 18 days), and 23 to 29 days (median, 26 days). Metabolic abnormalities were not observed in all patients during the TPN administration. There were no documented infections related to catheter placement. No patients required the removal of CV catheter until completion of TPN. Average weight loss was 1.4% (range, 0.8 to 1.8%) in group A and 3.4% (range, 0 to 7.6%) in group B, respectively. Serum albumin levels decreased by 0.37g/dL (range, 0.20 to 0.60g/dL) in group A and 0.07g/dL (range 0 to 0.10g/dL) in group B. The daily amount of fluid transfusion for patients in groups A and B were 88±11ml/kg and 73±10ml/kg during HCC, 63±1 ml/kg and 66±16 ml/kg until day 11 post-PBSCT, and 52±5 ml/kg and 55±11ml/kg by day 12 to 22 post-PBSCT, respectively. Drugs which could relieve vomiting were frequently prescribed for patients in both groups during HCC, but glucocorticoid was not administered through the treatment.

2. %REE during HCC and PBSCT (Fig.1)

For patients in group A, the %REE increased to 133±19% of BEE during HCC. At that time, their daily total energy intake was 61.5±18.0% of the actual REE. TPN, which was energy added to oral intake to meet REE, was initiated on day 0 of PBSCT and continued for 15 to 23 days. The %REE remained high at 128±14% until day 11 post-PBSCT and then markedly increased to 146±11% by day 12 to 22 post-PBSCT. This increase was closely related to recovery of bone marrow function.

For patients in group B, the %REE slightly increased to 114±12% during HCC. The total caloric intake during HCC was 90.6±11.7% of the measured REE for these patients. TPN supplementing REE was started on day -9 in case 4 and on day -7 in cases 5 and 6, i. e., one day before commencement of HCC, and continued for 23 days in patient 4, 29 days in patient 5 and 26 days in patient 6. Until day 11 following PBSCT, the %REE remained relatively constant at 111±10%. Interestingly, as was observed in group A, the %REE increased to 128±35% in these patients after 12 days of PBSCT and remained elevated for approximately one to two weeks. This increase also showed correlation with the recovery of marrow function.

%REE values in group A were significantly higher than those in group B during HCC until day 11 post-PBSCT ($p<0.001$).

3. RQ and substrate utilization rates during HCC and PBSCT (Fig.2 and Table 2)

For patients in group A, HCC suppressed the RQ to 0.786±0.047, and the RQ increased to 0.820±0.087 after the commencement of TPN and elevated significantly to 0.921±0.092 on days 12 to 22 of PBSCT compared with patients in group B ($p<0.005$). Further, the carbohydrate oxidation rate for patients in group A was significantly lower during HCC and the bone marrow aplastic period compared with patients in group B. Further, suppression of carbohydrate oxidation resulted in stimulation of fat oxidation and protein degradation during these periods. Then, when TPN was started, carbohydrate utilization increased significantly ($p<0.001$) with resultant decreased

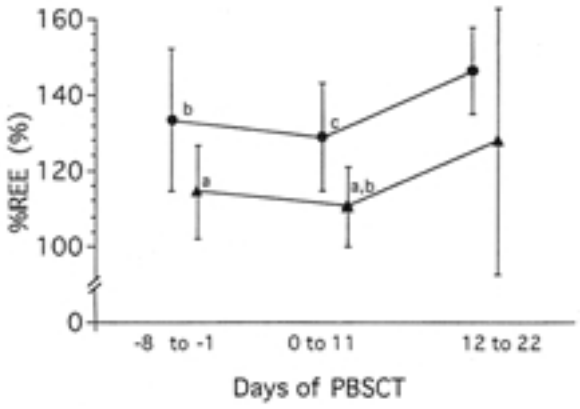

Fig.1. %REE during PBSCT procedure in patients of group A and group B.
● : Group A, ▲ : Group B
a : significantly different from group A (a : $p<0.001$)
b, c : significantly different from values in days 12 to 22 of PBSCT (b : $p<0.05$, c : $p<0.001$)

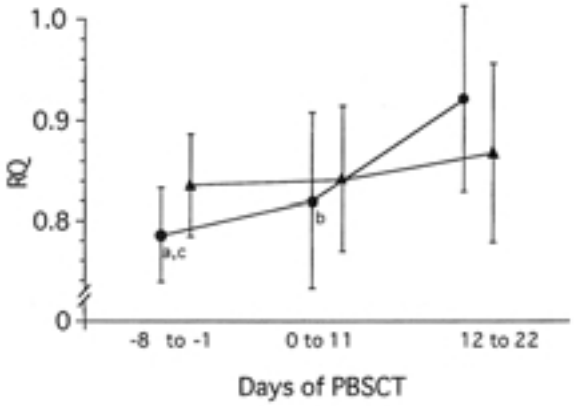

Fig.2. RQ during PBSCT procedure in patients of group A and group B.
● : Group A, ▲ : Group B
a : significantly different from group A (a : $p<0.005$)
b, c : significantly different from values in days 12 to 22 of PBSCT (b : $p<0.005$, c : $p<0.001$)

Table 2. The rates of substrate utilization during PBSCT treatment

	Carbohydrate (%)		Fat (%)		Protein (%)	
	Group A	Group B	Group A	Group B	Group A	Group B
-8 to -1	33.6±14.3 [f]	42.3±17.6 [b]	56.1±22.8 [e]	48.7±17.8	22.9±16.4 [c,e]	9.0±6.6 [a,d]
0 to 11	33.6±28.0 [e]	46.3±24.7	52.4±24.0	50.4±24.3	13.9±12.9	3.1±3.3 [b]
12 to 22	58.6±28.1	52.6±26.2	31.1±32.4	42.8±28.7	10.4± 6.8	4.6±4.4 [a]

a, b : significantly different from value of GroupA (a : $p<0.005$, b : $p<0.001$)
c : significantly different from value in days 0 to 11 of PBSCT (c : $p<0.05$)
d, e, f : significantly different from value in days 12 to 22 of PBSCT (d : $p<0.05$, e : $p<0.01$, f : $p<0.001$)

oxidation rates of fat and protein.

For patients in group B, the RQ during HCC showed 0.836±0.051, which was significantly higher than those in group A ($p<0.001$). The RQ values showed 0.842±0.072 and 0.868±0.089 on days 0 to 11 and days 12 to 22 following PBSCT. Utilization rates of carbohydrate and fat in each period of patients in group B remained nearly constant compared with those of patients in group A. However, the protein oxidation rate markedly decreased after commencement of TPN in both groups.

During HCC, the RQ value and carbohydrate oxidation rate in group A were significantly lower than those in group B ($p<0.001$).

DISCUSSION

The course of PBSCT can be divided into three periods, each presenting distinct metabolic challenge ; [1] HCC, [2] bone marrow aplasia, and [3] bone marrow recovery. HCC causes severe vomiting and painful mucositis in the oral pharynx and the esophagus, which hampered oral nutrition. Following cytoreduction, patients are profoundly neutropenic, which increases the risk of serious infection along with mucosal damage. Systemic effects of infection have appetite-suppressants, and nitrogen mobilization from protein breakdown is exacerbated by infection. After engraftment, mucosal lesions heal and patients are often able to resume oral intake. Several reports showed the efficacy of prophylactic TPN in bone marrow transplantation (BMT) to improve survival and reduce complications (12).

In this study, we attempted to evaluate the catabolic status and the effects of the timing of TPN commencement on the nutritional status of patients undergoing PBSCT using REE and RQ. Increased REE and protein degradation observed in patients in group A appeared due to HCC. Accelerated nitrogen degradation also appeared due to inadequate energy intake and a direct catabolic effect of chemotherapy. Furthermore, the substrate utilization pattern, with a decrease in carbohydrate oxidation and an increase in fat oxidation, was altered. For patients in group B, %REE and the protein oxidation rate during HCC and PBSCT were significantly lower than those in group A. Furthermore, the oxidation rates of carbohydrates and fat did not fluctuated greatly throughout the treatment period. These findings indicate that increased energy expenditure and nitrogen loss derived from HCC as well as the energy depletion observed in group A patients can be overcome by TPN initiated prior to HCC.

Increased fat utilization results either from hormonal changes that promote lipolysis or possibly from intracellular effects that promote fatty acid oxidation (13). Therefore, we hypothesize that the changes in substrate utilization were explained by the direct effects of the cytotoxic drugs as well as the energy depletion in the patients. In addition, the moderate increases in the REE that were observed between day 0 and 11 of post-PBSCT in group A patients might be explained by the influences of severe metabolic stress and inflammation resulting from the conditioning regimen and neutropenia. Since energy deficiency promotes fat oxidation, protein degradation and gluconeogenesis, %REE is enhanced suggesting that patients undergoing PBSCT were at serious risk of malnutrition. These findings are also consistent with the results of previous BMT studies which have demonstrated that aggressive chemotherapy and radiotherapy (14-16) in the conditioning regimens, and the duration of malabsorption caused by gastrointestinal lesions (6), can cause weight loss due to acute catabolism and the worsening of other anthropometric parameters (17).

The marked increase in REE and decrease in protein oxidation which we observed 12 to 22 days of post-PBSCT in both groups A and B are interesting. These increases occurred in conjunction with marrow recovery following approximately 10 days of marrow aplasia. The REE returned to its basal levels 3 to 4 weeks later, by which time gastrointestinal function had almost recovered. These findings strongly suggested that increased REE reflected the recovered and enhanced status of hematopoietic cell proliferation and metabolic improvements, and that bone marrow recovery required sufficient energy and nutrients. Increased REE following PBSCT might comprise an initial phase of severe metabolic stress resulting from aggressive chemotherapy, which is followed by a second marrow function recovery phase. Increased REE have been associated during bone marrow recovery in both groups, although the TPN per se did not stimulate REE as observed in group B.

Thus, nutritional assessment using indirect calorimetry is a useful tool in providing nutritional support for children undergoing PBSCT. It also assists individualizing nutritional support, and anticipating complications. In addition, we concluded that prophylactic TPN, i.e., started prior to HCC, for patients undergoing PBSCT have beneficial effects that maintain the metabolic and nutritional status and reduce serious complications.

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